MRD as a Surrogate Endpoint for Efficacy Evaluation of New Drugs in Very High Risk ALL: Lessons from Ph+ ALL

FDA Meeting; April 18th, 2012

Stephen P. Hunger, M.D.
Chair, COG ALL Committee
Professor and Ergen Family Chair in Pediatric Cancer
Director, Center for Cancer and Blood Disorders
Chief, Pediatric Hematology/Oncology/BMT
Univ of CO SOM and Children's Hospital Colorado
Aurora, Colorado USA

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Minimal Residual Disease (MRD) in COG AALL0232: 5-Year EFS

- End induction MRD burden is the strongest prognostic factor in recent pediatric ALL trials with very different outcomes for patients that attain different MRD levels at the end of the first month of therapy

Day 29 MRD level	5-Year EFS	SE	#pts (%)
<0.01%	86.4%	1.8%	1879 (72.4%)
0.01- <0.1%	74.9%	6.3%	291 (11.2%)
0.1- <1%	61.6%	8.8%	240 (9.2%)
1- <10%	51.3%	10.3%	130 (5.0%)
≥10%	26.8%	23%	56 (2.2%)

p<0.0001

Borowitz et al, ASH 2011

Can Early Response (MRD) Be Used to Assess Benefit of Interventions?

- May depend on trial design
  - Treatment A vs. Treatment B
  - Treatment A vs. Treatment A + drug X
  - Treatment A + drug X vs. Treatment A + drug Y
- Available data on A vs. B design not encouraging
  - AALL0232: Dex14 vs. Pred28 in pts <10 yr old
    - EFS advantage for Dex14 but no MRD difference

Pediatric Philadelphia Chromosome Positive (Ph^+) ALL

- About 3% of childhood ALLs are Ph^+
  - Rate begins to increase in late teens/early 20s
- Age, WBC and early response are important prognostic factors in Ph^+ ALL
- Dismal outcome for Ph^+ ALL in pre-imatinib era, with Ponte di Legno (PdL) group showing:
  - Matched sibling SCT better than chemotherapy (Arico NEJM 2000)
  - Any SCT better than chemotherapy (Arico, JCO 2010)

Outcomes in Ph+ ALL: Ponti Di Legno Group Analyses

Analyses limited to patients treated WITHOUT TKIs

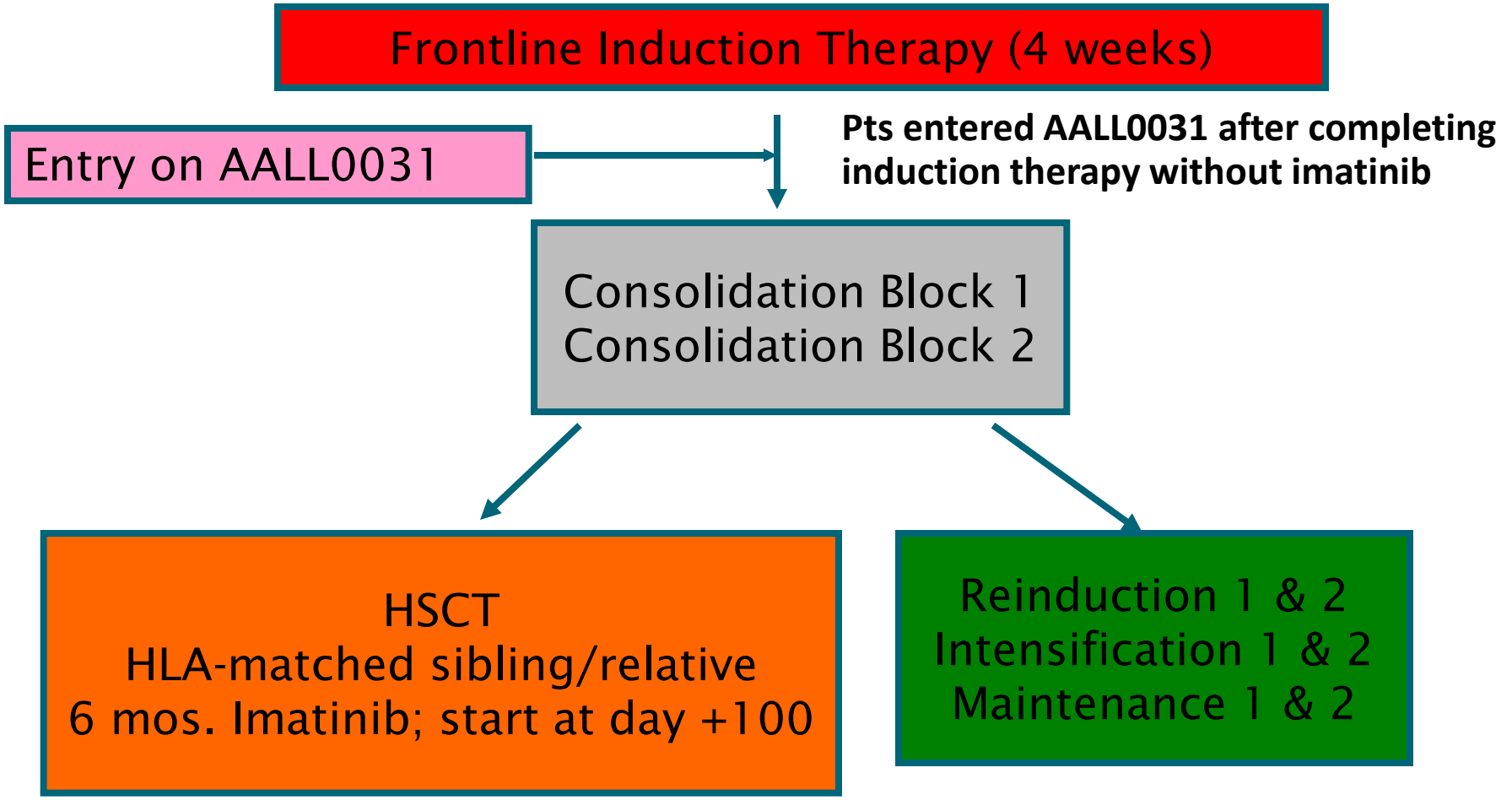
	1985-1996 (n=326)	1995-2005 (n=610)	p Value
CR rate	82%	89%	
7-yr EFS	25.0 +/- 3.0%	32.0 +/- 2.0%	0.0007
7-yr OS	36.0 +/- 3.0%	44.9 +/- 2.2%	0.017

Similar presenting features of patients in both cohorts

Outcome improved over time, but still poor without TKI therapy

Arico et al NEJM 2000 & JCO 2010

COG AALL0031: Treatment Schema



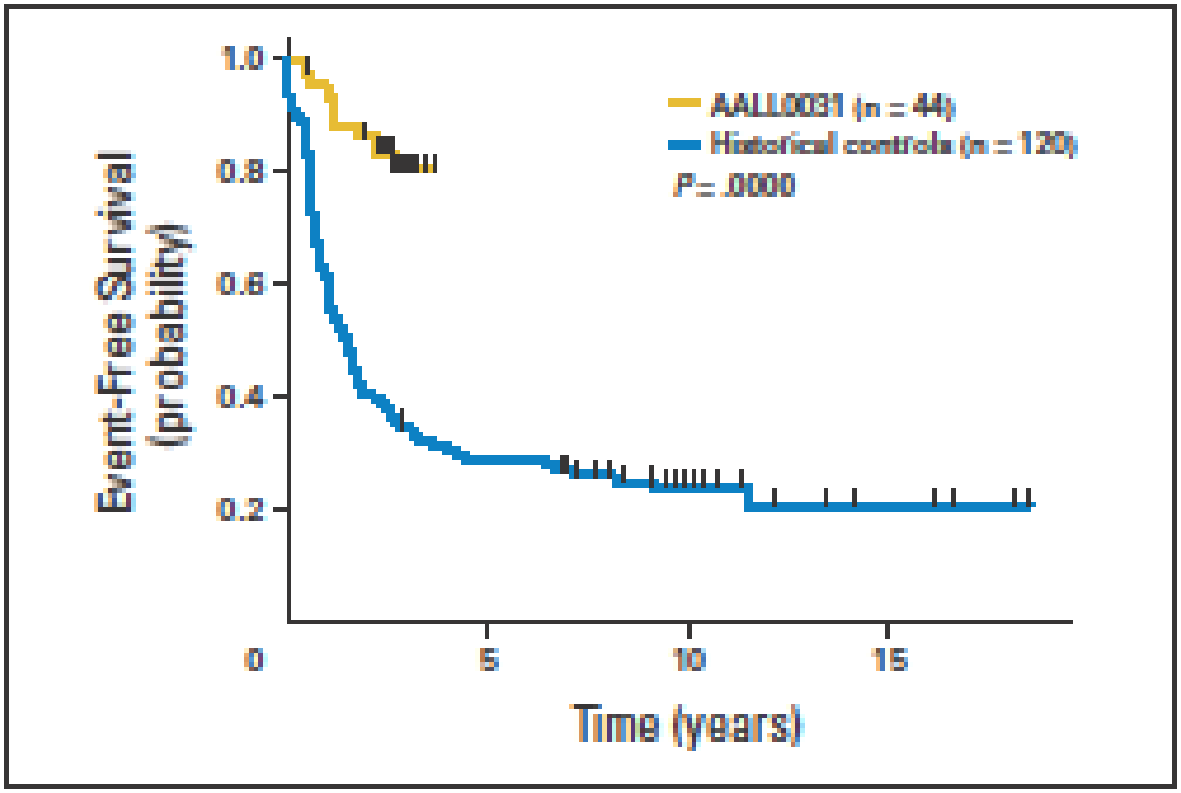
Schultz KR et al, JCO 27: 571, 2009

COG AALL0031: Improved Early EFS in Ph+ ALL with Imatinib + Chemotherapy

Therapy	Cons 1 (3 wk)	Cons 2 (3 wk)	Reind 1 (3 wk)	Intens 1 (9 wk)	Reind 2 (3 wk)	Intens 2 (9 wk)	Maint 1-4 (8-wk cycles)	Maint 5-12 (8-wk cycles)
Cohort 1				Imatinib x 3 wk		Imatinib x 3 wk	Imatinib x 3 wk	Imatinib x 2 wk every 4 wk
Cohort 2		Imatinib x 3 wk	Imatinib x 3 wk		Imatinib x 3 wk		Imatinib x 3 wk	Imatinib x 2 wk every 4 wk
Cohort 3	Imatinib x 3 wk →				Imatinib x 3 wk		Imatinib x 3 wk	Imatinib x 2 wk every 4 wk
Cohort 4	Imatinib x 3 wk →							Imatinib x 2 wk every 4 wk
Cohort 5	Continuous dosing of imatinib							Imatinib x 2 wk every 4 wk

Schultz KR et al, JCO 27: 571, 2009

AALL0031 Cohort 5 vs. Historical Controls



3-yr EFS

AALL0031c5

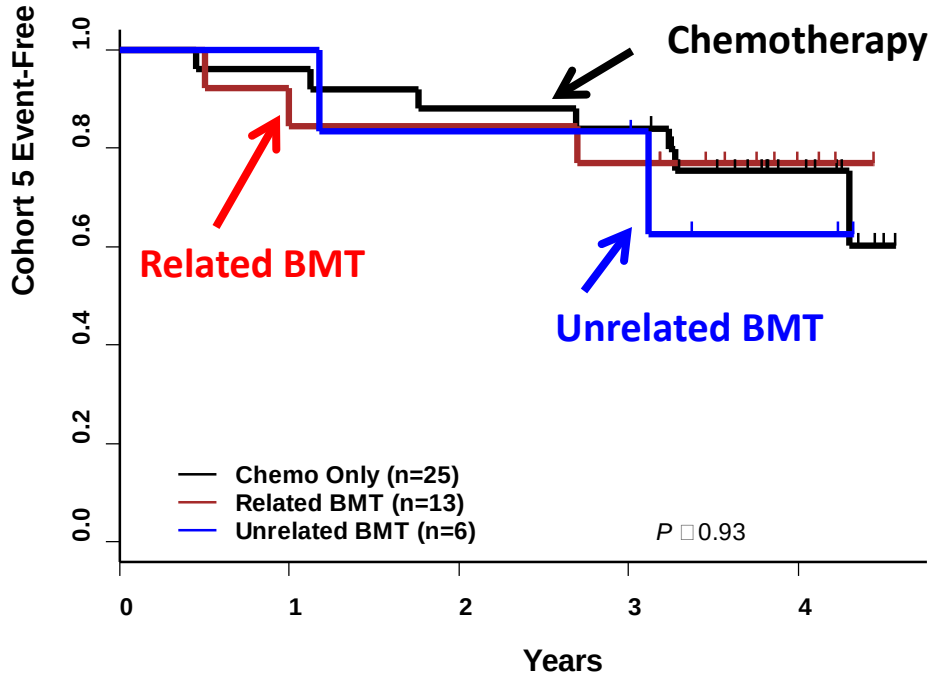
80.5% +/- 11.2%

POG ALinc 14-16

35.0% +/- 4.4%

Schultz KR et al, JCO 27: 571, 2009

Chemotherapy vs. MRD or URD BMT: COG AALL0031 Cohort 5



Cohort 5 + imatinib 84±7%
Related BMT 77%±12%
Unrelated BMT 83%±15%
P = 0.93

Schultz KR et al, JCO 27: 571, 2009

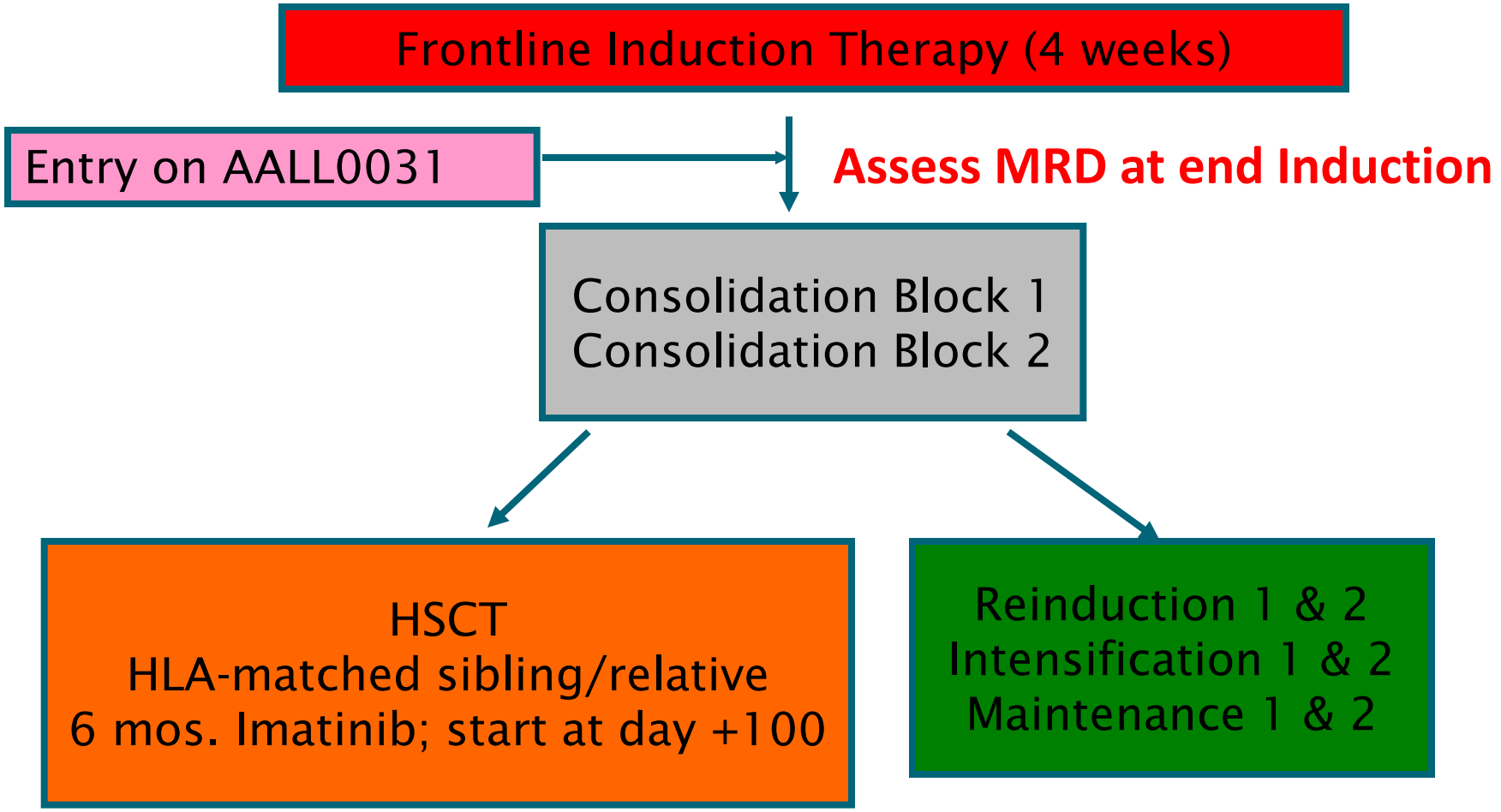
AALL0031: Implications

- Outstanding early outcome of intensive chemotherapy + imatinib in pediatric Ph^+ ALL
- Follow-up short, but excellent outcome for cohort 5 patients continues; all pts completed therapy by early 2009
- No evidence that SCT superior to chemo + TKI
- Suggests that further improvements will come through optimizing TKI therapy, not the chemotherapy regimen or SCT
  - Elected to test dasatinib, a more potent ABL TKI, in successor trial AALL0622

TKI Therapy: AALL0031 vs. AALL0622

- AALL0331
  - Imatinib started at day 1 Consolidation
- AALL0622 (same chemo as AALL0031)
  - Dasatinib started at day 15 Induction
    - Discontinuous (2 wks/cycle) in 41 pts
    - Continuous in 16 pts
- Provides opportunity to compare
  - Effect of dasatinib added to chemo in induction
  - Effect of dasatinib vs. imatinib on later response
    - Confounded by discontinuous dasatinib in most 0622 pts

COG AALL0031: Treatment Schema



Schultz KR et al, JCO 27: 571, 2009

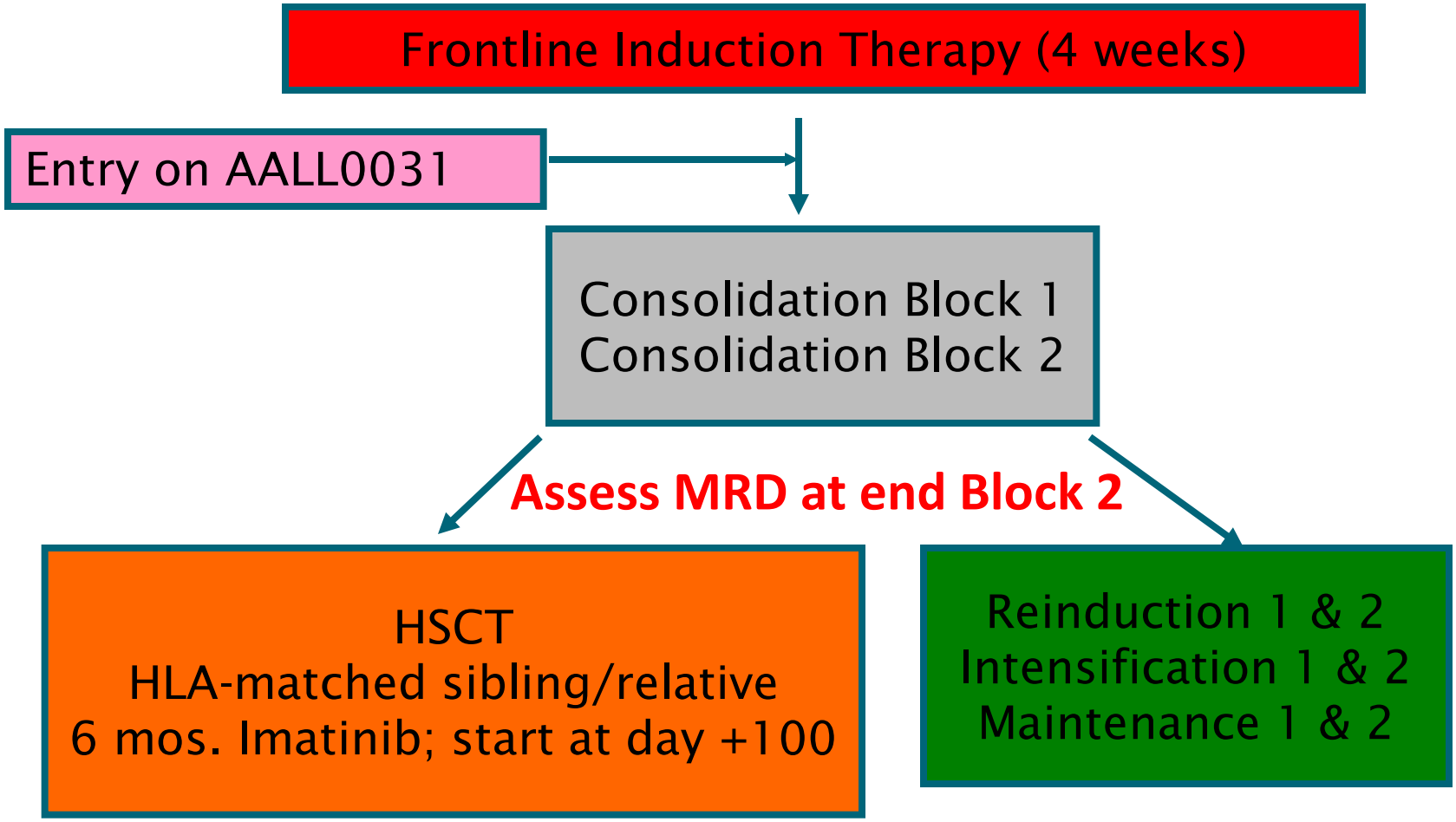
AALL0622 End Induction Response

Slayton, Submitted for SIOP 2012

	AALL0331 No TKI during induction	AALL0622 Dasatinib days 15-29	P Value
Day 29 M1	89%	98%	0.0148
Day 29 MRD <0.01%	25%	59%	<0.01

- Dasatinib significantly increased remission (M1) rate and decreased end induction MRD burden
- What would regulatory implications be if this had been a randomized trial of induction chemo +/- dasatinib?

COG AALL0031: Treatment Schema



Schultz KR et al, JCO 27: 571, 2009

AALL0622 End Block 2 Response

Slayton, Submitted for SIOP 2012

	AALL0331 Continuous imatinib during blocks 1 + 2	AALL0622 Dasatinib 2 wks induction and 2/3 discontinuous and 1/3 continuous in blocks 1 +2	P Value
End Block 2 MRD <0.01%	**75%**	**89%**	**0.037**

- **Dasatinib significantly increased MRD negative rate, suggesting it is a better TKI than imatinib for Ph^+ ALL**
- **What would regulatory implications be if this had been a randomized trial of chemo + imatinib vs. chemo + dasatinib?**

Acknowledgements

- Mauricio Arico and PdL group
- Kirk Schultz
- William Slayton
- Mini Devidas
- William Carroll
- Naomi Winick
- Elizabeth Raetz
- Mignon Loh